Status Epilepticus
A Neurologic Emergency

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KEYWORDS

• Status epilepticus • Seizure • Electroencephalography • Antiseizure drugs
• Brain injury • Neurocritical care

KEY POINTS

- Status epilepticus is a common neurologic emergency defined as abnormal, prolonged seizures lasting greater than 5 to 10 minutes, or recurrent seizure activity without recovery to the patient's baseline mental status.
- First-line treatment of status epilepticus is benzodiazepines, with multiple second-line agents available.
- Refractory and super refractory status epilepticus are defined as continued seizure activity despite administration of appropriate doses of initial and second-line therapies and medication-refractory seizure activity lasting longer than 24 hours, respectively.
- Many conditions can cause new onset status epilepticus, mandating a broad diagnostic evaluation.

INTRODUCTION

Status epilepticus (SE) is a life-threatening emergency requiring rapid treatment and diagnostic evaluation. Initial interventions include administration of medications to terminate seizures, early empiric management of presumed causes, cardiopulmonary monitoring, and potentially mechanical ventilation and other organ support. In the United States, SE develops most commonly in outpatients and is initially encountered by prehospital and emergency providers. Inpatients may also develop SE (either convulsive or nonconvulsive) as a complication of acute illness with or without a primary neurologic injury. Diagnosis requires a high index of suspicion and electroencephalography (EEG) monitoring.

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Here, we provide an overview of SE pathophysiology, diagnostic criteria, treatments, etiologies, and specific considerations based on underlying cause. We focus on several patient populations with unique clinical considerations including undifferentiated intensive care unit (ICU) patients, patients with acute brain injury, toxicity, autoimmune conditions, pediatrics, and pregnancy.

PATHOPHYSIOLOGY AND CRITERIA

Seizures are abrupt, synchronous, and pathologic depolarizations of cortical neurons that can affect a single region (focal) or the entire brain (generalized). Manifestations of focal seizures vary based on the function of affected cortex and include decreased level of consciousness, visual changes, automatisms, and tonic-clonic movements.[1] Nonconvulsive seizures (NCS) may have subtle clinical findings. NCS and nonconvulsive status epilepticus (NCSE) are more common with a history of epilepsy, persistent altered mental status, and acute brain injury.[2] Most seizures are self-terminating because of protective cellular, local, and remote network mechanisms.[3] Failure of these mechanisms marks a critical transition where neuronal inflammation, blood–brain barrier dysfunction, endocytosis of drug-sensitive gamma-aminobutyric acid (GABA) subunits, and shuttling of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartic acid (NMDA) receptors toward the synapse propagate further synchronization and seizure activity.[4] Thus antiseizure drug (ASD) responsiveness decreases over time.[5–7] Seizures longer than 5 minutes are less likely to terminate without ASDs.[8] Brain injury worsens with longer seizure duration, ultimately resulting in cell death.[9]

The International League Against Epilepsy defines SE as abnormally prolonged seizures greater than 5 minutes in the presence of generalized tonic-clonic activity, greater than 10 minutes of focal seizures with impaired consciousness and greater than 10 to 15 minutes of absence seizures.[10] The Neurocritical Care Society defines SE as 5 or more minutes of continuous clinical and/or electrographic seizures, or recurrent seizure without recovery to baseline.[11] The American Clinical Neurophysiology Society (ACNS) Critical Care EEG Terminology offers standardized definitions of electrographic and electroclinical SE.[12]

EPIDEMIOLOGY

The reported incidence of SE in the United States has increased from 3.5 to 41 per 100,000 during the past 35 years.[13] Increased awareness, availability of EEG monitoring, and better long-term survival of patients with chronic conditions that predispose to seizure are contributing factors. SE presents a significant financial and logistical burden to the health-care system. The average length of stay for SE is 2 weeks, whereas for refractory-(RSE) and super-refractory status epilepticus (SRSE), the average length of stay is weeks to months.[14,15] Mortality estimates vary based on underlying cause.[16] Multiorgan failure, preexisting functional dependence, advanced age, and resistance to treatment predict worse outcomes.[17] Withdrawal of life-sustaining therapies for perceived poor prognosis is a significant contributor to mortality.[18] Among long-term survivors, risk of recurrent SE maybe as high as 55%.[19]

INITIAL TREATMENT

Protocols for SE treatment should exist for hospitals or health-care systems. **Fig. 1** is a modified version of our local protocol. Benzodiazepines are the recommended initial

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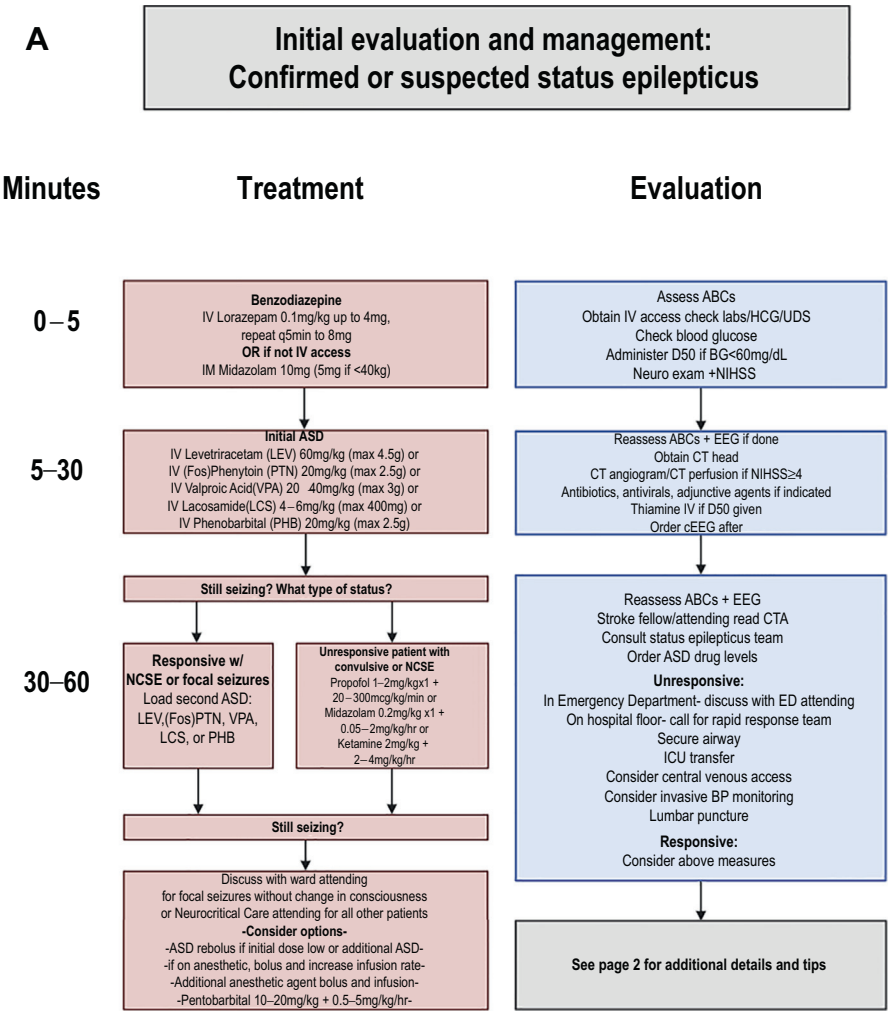

Fig. 1. (*A*) Example status epilepticus treatment and diagnosis protocol and (*B*) additional helpful references. (Created with Biorender.com.)

abortive therapy.[11,20] In the Veterans Affairs cooperative trial, lorazepam (LZP) was equivalent to both phenobarbital (PHB) and diazepam (DZP) followed by phenytoin (PHT), and more efficacious than PHT alone, in achieving clinical and/or electrographic seizure control within 20 minutes and no recurrent activity within 60 minutes of treatment. LZP administration was faster than other treatment arms. Regardless of therapy, successful seizure termination occurred in two-thirds of subjects.[21]

When adult patients with greater than 5 minutes of continuous seizure activity in the prehospital setting received either 2 mg intravenous (IV) LZP, 5 mg IV DZP, or placebo, with the option for second dose if needed, SE terminated before emergency department arrival in 59%, 42%, and 21% of patients, respectively.[6] Moreover, administration of 10 mg of intramuscular midazolam (MDZ) is noninferior to 4 mg IV LZP.[22] Subtherapeutic dosing of benzodiazepines is common and associated with treatment

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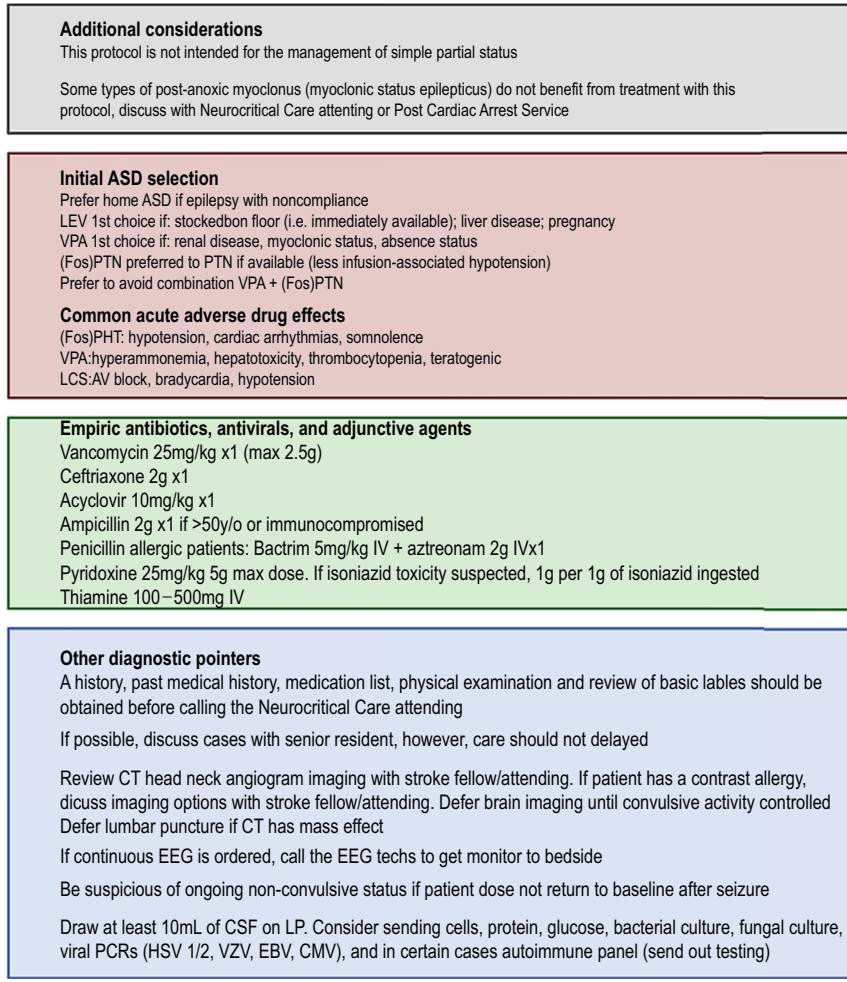
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Additional considerations
This protocol is not intended for the management of simple partial status
Some types of post-anoxic myoclonus (myoclonic status epilepticus) do not benefit from treatment with this protocol, discuss with Neurocritical Care attenting or Post Cardiac Arrest Service
Initial ASD selection
Prefer home ASD if epilepsy with noncompliance
LEV 1st choice if: stockedbon floor (i.e. immediately available); liver disease; pregnancy
VPA 1st choice if: renal disease, myoclonic status, absence status
(Fos)PTN preferred to PTN if available (less infusion-associated hypotension)
Prefer to avoid combination VPA + (Fos)PTN
Common acute adverse drug effects
(Fos)PHT: hypotension, cardiac arrhythmias, somnolence
VPA:hyperammonemia, hepatotoxicity, thrombocytopenia, teratogenic
LCS:AV block, bradycardia, hypotension
Empiric antibiotics, antivirals, and adjunctive agents
Vancomycin 25mg/kg x1 (max 2.5g)
Ceftriaxone 2g x1
Acyclovir 10mg/kg x1
Ampicillin 2g x1 if >50y/o or immunocompromised
Penicillin allergic patients: Bactrim 5mg/kg IV + aztreonam 2g IVx1
Pyridoxine 25mg/kg 5g max dose. If isoniazid toxicity suspected, 1g per 1g of isoniazid ingested
Thiamine 100−500mg IV
Other diagnostic pointers
A history, past medical history, medication list, physical examination and review of basic lables should be obtained before calling the Neurocritical Care attending
If possible, discuss cases with senior resident, however, care should not delayed
Review CT head neck angiogram imaging with stroke fellow/attending. If patient has a contrast allergy, dicuss imaging options with stroke fellow/attending. Defer brain imaging until convulsive activity controlled
Defer lumbar puncture if CT has mass effect
If continuous EEG is ordered, call the EEG techs to get monitor to bedside
Be suspicious of ongoing non-convulsive status if patient dose not return to baseline after seizure
Draw at least 10mL of CSF on LP. Consider sending cells, protein, glucose, bacterial culture, fungal culture, viral PCRs (HSV 1/2, VZV, EBV, CMV), and in certain cases autoimmune panel (send out testing)

Fig. 1. (*continued*)

failure and progression to RSE.[23–26] Although respiratory compromise is a concern, a trend toward fewer respiratory complications with adequate dosing is reported.[27]

SECOND-LINE INTERMITTENT ANTISEIZURE DRUGS

Second-line ASDs are administered to all SE patients regardless of benzodiazepine response to prevent seizure recurrence. Options include PHT, valproic acid (VPA), levetiracetam (LEV), PHB, or lacosamide (LCS). The Established Status Epilepticus Treatment Trial (ESETT) was the largest randomized trial of PHT, VPA, and LEV for adults and children with benzodiazepine-refractory SE.[28] The trial was stopped early for equivalence, with no difference in primary outcome of cessation of seizures and improving mental status within 60 minutes of medication administration, or safety profile. LCS has similar efficacy compared with PHT, although it has been tested in fewer patients.[29] In a recent meta-analysis, PHB was the most effective second-line ASD,

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Table 1
Considerations for choosing an anesthetic infusion

Anesthetic Infusion	Considerations
Midazolam	• Favorable hemodynamic profile[115] • Tachyphylaxis with infusions >24–48 h[116] • May deposit into adipose, cause prolonged sedation[116]
Propofol	• Rapid drug clearance • May cause dose dependent hypotension, myocardial depression • Propofol infusion syndrome (PRIS) with extended use and in children
Ketamine	• N-methyl-D-aspartate (NMDA) blockade is unique mechanism compared with other anesthetic options • Favorable hemodynamic profile and intracranial hypertension concerns not observed in contemporary work[117] • Unclear half-life in high dose, prolonged infusions • Less studies compared with other agents
Pentobarbital	• Reserved for cases where other anesthetic options fail to control seizures • Prolonged half-life in adults[118] • Cardiac depression, bone marrow suppression, ileus[119,120]

Data from Refs.[115–120]

followed by VPA, LCS, LEV, and finally PHT. However, the most cost-effective was LEV, followed by VPA, then PHB. Neither LSC, nor PHT were cost-effective.[30] Our practice is to administer the medication that is most rapidly available with secondary consideration of potential adverse effect profiles, drug–drug interactions, and past medical history.

REFRACTORY STATUS EPILEPTICUS

Seizures that continue after adequate doses of first-line and second-line ASDs are deemed RSE. Based on expert opinion, guidelines suggest intubation and seizure

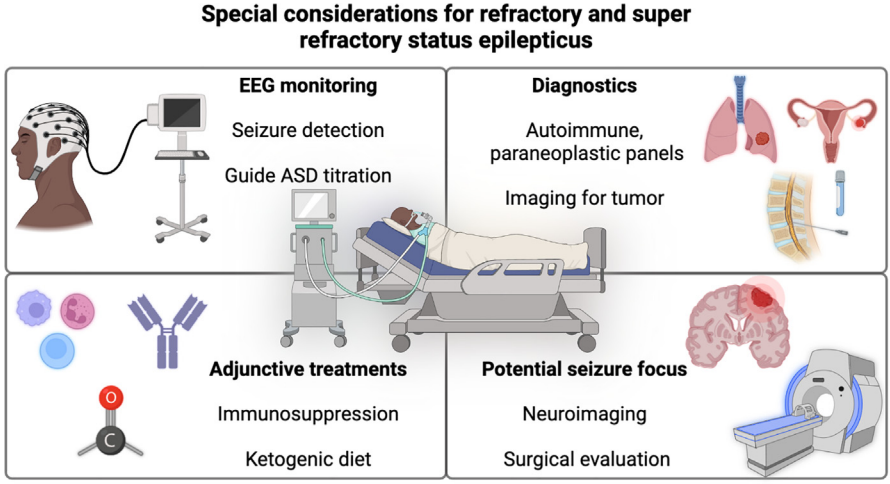

Fig. 2. Failure of conventional antiseizure drugs should prompt additional workup and treatment. (Created with Biorender.com.)

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suppression with anesthetics for SE continuing 20 to 60 minutes after loading a second-line ASD. Several medications are effective in this setting, with little data available to guide optimal choice (Table 1). EEG monitoring is needed to detect ongoing NCS and to guide titration of anesthetic infusions to effect, with options for seizure control, burst suppression, or isoelectric suppression.[31] Loading a third ASD before considering intubation may be reasonable in patients with advanced directives limiting aggressive care, when there is clinical suspicion for a rapidly reversible cause such as hypoglycemia, or ASD noncompliance.

Super Refractory Status Epilepticus

Patients who continue to seize for greater than 24 hours despite stepwise escalation of therapies qualify as SRSE. Evidence-based treatments of SRSE are limited to case reports and series (Fig. 2). Both those with known history of epilepsy and new-onset refractory status epilepticus (NORSE) require special consideration in their diagnostic evaluation. Combinations of mechanistically distinct ASDs may provide synergism. Ketogenic diet shifts neurons from glucose to lipid metabolism and has antiseizure effects. Data for use of ketogenic parenteral nutrition in SRSE are limited but present a promising area for future studies.[32] Inhaled anesthetics are an option when feasible.[33] Therapeutic hypothermia (32°C–34°C) for 24 hours decreased the incidence of EEG confirmed SE without benefit to 90-day mortality and had a higher incidence of adverse events.[34] Brain MRI or ictal single photon emission computed tomography may identify lesions amenable to surgery.[35] Empiric immune therapy for suspicion for autoimmune conditions is recommended. Treatment within 30 days of onset is associated with better functional status.[36] Options include high-dose corticosteroids, intravenous immunoglobulins, plasma exchange, rituximab, or cyclophosphamide.[37] Devices such as vagal nerve stimulators, responsive neurostimulation systems, transcranial magnetic stimulators, and electroconvulsive therapy have had some effect in case series but little randomized data.[38]

DIAGNOSTIC EVALUATION

Many acute and chronic medical conditions can cause SE. The initial diagnostic workup is broad and occurs in parallel with stabilization and ASD administration (Fig. 1). Patients with potential SE require continuous telemetry and pulse oximetry, as well as close serial airway assessments. Capillary blood glucose should be measured immediately and hypoglycemia corrected. Vascular access should be obtained urgently to facilitate administration of ASDs and obtain bloodwork. A comprehensive metabolic panel will identify common metabolic derangements. Urine toxicology for all and beta-hCG in women of childbearing age is standard. ASD levels may be drawn for concerns of nonadherence but should not delay treatment.

Physical examination should screen for findings suggestive of acute traumatic brain injury (TBI), stroke, or other intracranial cause of seizures. Urgent noncontrast head CT is pursued in all patients unless rapid return to baseline occurs in combination with a nonfocal examination and known history of epilepsy. CT angiography of the head and neck is considered for new focal neurologic deficits or persistent coma because acute ischemic stroke (AIS) may mimic or precipitate seizure.[39–41] Lumbar puncture is indicated when history suggests infection, or for new onset or unprovoked seizure. Cerebrospinal fluid (CSF) analysis of at minimum cell counts, glucose, protein, Gram stain and culture, and herpes simplex PCR assay is recommended. Additional CSF is often obtained for diagnosis of autoimmune, paraneoplastic or other viral encephalitides.[37] Antibiotics and antivirals should be administered

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without delay to avoid poor outcomes.[42] Finally, SE with obvious clinical manifestations often evolves into NCSE. Apparent resolution of clinical seizures in the absence of return to neurologic baseline should be treated as NCSE until proven otherwise with EEG monitoring.[43]

The need for more comprehensive diagnostic evaluation is guided by treatment responsiveness and presumed cause of seizures. For patients who return to baseline cognition after benzodiazepine administration and for whom history suggests a clear cause (eg, alcohol withdrawal seizures, epilepsy with ASD nonadherence, or hypoglycemia), routine bloodwork and telemetry monitoring may suffice.

When risk for SE is high, continuous EEG (cEEG) monitoring is preferred over intermittent EEG. cEEG reaches 95% sensitivity for seizure detection at 72 hours of monitoring, reduces time to diagnosis, and affords safe medication titration.[44–47] Initial characteristics of background and presence of epileptiform features may aid in triaging need for cEEG when resources are limited. Negative history of seizures and generalized slowing without epileptiform features are associated with low risk of seizures during extended monitoring. In contrast, epileptiform discharges or burst suppression on initial EEG have greater than 30% incidence of seizures on cEEG.[48]

SPECIFIC POPULATIONS

General Intensive Care Unit Patients

Patients with SE are at high risk for complications in the ICU due to prolonged critical illness, mechanical ventilation, seizure etiology, and ASD toxicities.[49,50] Immobility increases the incidence of decubitus ulcers, deep vein thrombosis, and nosocomial infections. Aggressive pulmonary toilet may mitigate atelectasis, mucous plugging, and pneumonia. Ileus is common and should be suspected in constipation and increased gastric residual volumes.[51] ASDs have numerous potential adverse effects. Drug–drug interactions can alter levels of ASDs or other medications; a single dose of a carbapenem may rapidly reduce VPA concentration to undetectable serum levels.[52] Optimal management of patients with RSE and SRSE is best achieved through a multidisciplinary team with neurocritical care and pharmacologic expertise.

SE may also result from general critical illness. Systemic inflammation in sepsis decreases seizure threshold and carries a seizure incidence of 10% to 20%.[53–55] Risk factors include severity of illness and past neurologic diagnosis.[56] Beta-lactam antibiotics competitively inhibit GABA receptors in a dose-dependent fashion, thus increasing seizure risk.[57] Although cefepime neurotoxicity is most reported, other cephalosporins with good central nervous system penetration such as ceftriaxone and ceftazidime also demonstrate neurotoxicity.[58] Evolving renal or hepatic injury may increase drug levels and exacerbate neurotoxicity.

STATUS EPILEPTICUS COMPLICATING ACQUIRED BRAIN INJURY

Ischemic and Hemorrhagic Strokes

Both hemorrhagic and ischemic strokes can be complicated by seizures. In intraparenchymal and subarachnoid hemorrhage, blood acts as a cortical irritant.[59] After AIS, metabolic failure, tissue hypoxia, and reperfusion injury can precipitate seizures. NCS are common, occurring in 3% in AIS to 13% in aneurysmal subarachnoid hemorrhage.[60,61] Seizure should be considered in stroke patients with unexpectedly poor (ie, out of proportion to imaging findings), fluctuating, or suddenly worsening neurologic examination.[62] Hemorrhagic conversion, rebleeding, and delayed cerebral ischemia/vasospasm are all potential causes of seizures and SE.

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Traumatic Brain Injury

Severe TBI frequently leads to NCS and SE, with intracranial hemorrhage and penetrating injury significantly increasing seizure risk.[63] Seizures may precipitate metabolic and/or intracranial pressure crises in TBI patients, so cEEG monitoring is critical.[64]

Hypoxic Ischemic Brain Injury

Up to half of comatose postcardiac arrest patients have epileptiform EEG findings.[65,66] Incidence of seizures and SE maybe as high as 30% and 12%, respectively,[67,68] although variability in monitoring strategies and nomenclature exist.[45,47] EEG patterns that represent treatable epileptiform events versus secondary manifestations of severe brain injury are controversial. Burst suppression with identical bursts in time step lock with myoclonus meets criteria for electroclinical seizures, often does not respond to conventional ASDs, and is associated with diffuse cortical and subcortical necrosis on autopsy.[66,69] Treating seizures is recommended although aggressive treatment of periodic or rhythmic patterns that do not meet ACNS seizure criteria does not improve outcome.[70] Choice of ASD agent is driven by cardiac, hemodynamic, and other organ failure considerations.

Autoimmune Causes

Patients who present with SRSE, NORSE, or febrile infection-related epilepsy syndrome (seizure onset within 2 weeks of febrile illness, FIRES) warrant specific consideration of immunologic causes. Approximately 50% of NORSE or FIRES cases are autoimmune or paraneoplastic in etiology.[71] Early neurocritical care and neuroimmunology consultation is advised.[72] Whole-body cross-sectional imaging and transvaginal ultrasound may reveal immune active teratomas amenable to surgical resection or malignant source of paraneoplastic syndrome. Targeted immune therapies including anakinra and tocilizumab have been studied in small case series but no randomized controlled trials (RCTs) have been performed to date.[73,74] Patients with cancer often present with or develop altered mental status during hospitalization.[75] Although the differential is broad, SE is a potential cause. Checkpoint inhibitors and chimeric antigen receptor T cell therapy in particular are epileptogenic.[76,77]

Toxicologic

Seizures related to toxidromes may be overdose or withdrawal induced[78] from either abnormal excitation or loss of inhibition. Alcohol withdrawal is the most common toxicologic cause.[79] Consistent alcohol use modulates density of numerous neuronal ion channels, including upregulation of $GABA_a$ and glycine and inhibition of NMDA receptors.[80,81] Cessation of alcohol without medications or doses insufficient to maintain sufficient GABAergic tone results in excitotoxicity.

Clinical trials have focused on alcohol withdrawal syndrome and symptom management rather than seizures. A single RCT found PHT no better than placebo for seizure control.[82] Benzodiazepines are again recommended as initial therapy. Mechanistically, PHB and ketamine are attractive alternative agents for patients who fail initial benzodiazepine therapy or require escalating doses. In addition to GABAa agonism, PHB inhibits excitatory AMPA and Kainate receptors. Moreover, PHB's long half-life affords ease of titration and autotapering for prolonged control. Compared with benzodiazepines and barbiturates, ketamine binds to multiple sites of NMDA receptors that are inhibited in chronic alcoholism. Dexmedetomidine has gained popularity for autonomic symptom management but has no antiseizure properties.[83]

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Bupropion is an antidepressant favored for being weight-neutral and aiding in smoking cessation. Chemically, bupropion decreases reuptake of dopamine and norepinephrine from synapses, which may cause uninhibited postsynaptic excitation.[84] Selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors have similar mechanisms and have minimal risk of seizures except in overdose situations.[85] Baclofen is a synthetic GABA agonist, and withdrawal or overdose may lead to seizure, the latter through presynaptic inhibition and subsequent postsynaptic disinhibition.[86,87] Baclofen toxicity must be considered in patients with in situ intrathecal drug delivery systems.[88] Pyridoxine is a cofactor critical for GABA synthesis, and deficiencies can occur with chronic isoniazid use or overdose,[89] malnutrition or marasmus,[90] Gyromitra esculenta ingestion,[91] and hydrazine exposure.[92] Early empiric pyridoxine is indicated when suspicion of deficiency exists. Apart from pyridoxine indications and thiamine administration in alcoholics, seizures related to intoxication or withdrawal is preferentially managed with GABAergic agents. Little data are available regarding second line agents in this population.[93]

Pediatrics

The initial treatment of pediatric patients presenting with SE is similar to that of adults. Benzodiazepines remain first-line treatment. In patients without intravenous access, intranasal MDZ is more efficacious than rectal DZP.[94] There is no clearly preferred second-line ASD in children. PHT and LEV were equally effective in 2 large RCTs.[95,96] In pediatric patients, no treatment arm was superior in the ESETT trial.[97] VPA is avoided in children with mitochondrial hepatopathies because a single dose can precipitate fulminant liver failure.[98] Pyridoxine-dependent epilepsy is rare but an important cause of pediatric SE; supplementation is recommended when second-line ASDs fail.[99] Propofol is avoided given risk of propofol infusion syndrome and potential fatal reactions in children. MDZ and PHB are preferred third-line ASDs. Ketamine is under active investigation but not yet guideline-recommended.[100,101]

Pregnancy

Preeclampsia is a syndrome of hypertension, proteinuria, and headache after 20-week gestation.[102] Eclampsia is the new onset of generalized seizure in the setting of preeclampsia, and the most common cause of SE in pregnancy.[103] It is a clinical diagnosis that has been reported up to 23 days postpartum.[104] IV magnesium is standard of care for prophylaxis and treatment of eclamptic seizures,[105–107] and neuroimaging is indicated in patients unresponsive to initial treatments. Eclamptic seizures may share pathogenesis with posterior reversible encephalopathy syndrome, where inflammation, hypertension, and deranged cerebrovascular autoregulation contribute to blood–brain barrier permeability, vasospasm, and vasogenic edema.[108,109]

Alterations in cardiac output, renal perfusion, volume of distribution, and serum protein levels in pregnancy affect ASD pharmacokinetics.[110] However, similar rates of breakthrough seizure are reported in pregnant versus nonpregnant patients with epilepsy.[111] Closer monitoring of serum drug levels is recommended.[112] Lamotrigine, LEV, and oxcarbazepine seem to have similar teratogenicity to controls, whereas carbamazepine and VPA at any dose are associated with congenital anomalies.[113] Apart from magnesium for eclampsia, there are no RCTs specific to SE in pregnancy. ASD choice is influenced by gestational age, prior ASD use, and potential adverse effects in consultation with epileptology and maternal and fetal medicine specialists.[114]

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SUMMARY

SE is encountered as a presenting illness, complication of various primary brain injuries, and many seemingly nonneurological illnesses. Although expert consultation is recommended, all providers should be versed in the identification, evaluation, and early treatment of seizures to prevent time-dependent treatment resistance. A high index of suspicion, prompt diagnosis, and treatment targeted to specific causes contribute to improved outcomes in this complex disease.

CLINICS CARE POINTS

- Benzodiazepines are first-line treatment of status epilepticus. Subtherapeutic dosing of benzodiazepines is common and associated with treatment failure.
- Many second-line antiseizure drugs are available. Our practice is to administer the agent that is most rapidly available with secondary consideration of potential adverse effect profiles, drug–drug interactions, and past medical history.
- Antiseizure drugs have complex interactions with other antiseizure and commonly used drugs in the intensive care unit. Comanagement with a pharmacist with neurocritical care expertise is vital.
- Seizures refractory to first-line and second-line antiseizure drugs should prompt a broad diagnostic workup and expert consultation.

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DISCLOSURE

None.

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